Arabian Journal of Chemistry (2014) xxx, xxx–xxx

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Facile and efficient synthesis of benzoxazole derivatives using novel catalytic activity of PEG-SO_3H

Rupesh V. Chikhale *, Amit M. Pant, Sunil S. Menghani, Pankaj G. Wadibhasme, Pramod B. Khedekar

Computer Aided Drug Design Laboratory, Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Mahatma Jyotiba Fuley Shaikshanik Parisar, Amravati Road, Nagpur 440033, India

Received 21 December 2012; accepted 23 June 2014

KEYWORDS

Poly (ethylene glycol)-bound sulfonic acid (PEG-SO_3H); 2-Aminobenzoxazole; Benzoxazole derivatives

Abstract A highly efficient, simple and rapid method for the preparation of various 2-aminobenzoxazoles and other benzoxazole derivatives using a catalytic amount of poly (ethylene glycol)-bound sulfonic acid (PEG-SO_3H) is described. PEG-SO_3H is found to be an economical and reusable catalyst with low catalytic loading. The percent yield was found to be satisfactory, experimental set up and purification of final products are facile and easy.

1. Introduction

Benzazoles like benzoxazole, benzothiazole and benzimidazole derivatives are of immense importance in chemical (Yoshida et al., 2005), agrochemical dye-stuff (Tian and Ling, 2007), polymer (Vicini et al., 2008) and pharmaceutical industries (Murugesan et al., 2009). These compounds have a broad spectrum of biological and pharmacological activities such as antihypertensive (Vicini et al., 2003), antiepileptic (Jain et al., 2007), antimicrobial (Walczynski et al., 1999), phosphodiesterase inhibitor (Tsurumi et al., 1973), neuropeptide binding (Siddiqui et al., 2007), antiviral (Yildiz-Oren et al., 2004) and pesticidal activity (Mccracken and Stillwell, 1991). Benzoxazole and its derivatives like 2-aminobenzoxazole find extensive therapeutic importance in medicine for indications such as neural disorders (Wang et al., 2007), antineoplastic (O'Donnell et al., 2010), anti-inflammatory (Cheung et al., 2002), treatment of metabolic disorders (Clark et al., 2000), irritable bowel syndrome (IBS) (Muller et al., 1999), antiviral (Sato et al., 1997), thrombolytic (Surleraux et al., 2002) and sleep disorders (Laibekman et al., 2003). The classical route for the synthesis involves nucleophilic displacement of a 2-substituted benzoxazole, 2-substituents include Cl (Cox et al., 2010), SH (Seefelder and Leuchs, 1962) and SCH_3 (Katz and Cohen, 1954) or OPh (Yamato et al., 1984) with an amine. Drawbacks of these routes include penultimate intermediates that involve multiple steps to prepare, utilization of harsh reagents and conditions,

* Corresponding author. Tel.: +91 8983387871.
E-mail address: rupeshchikhale7@gmail.com (R.V. Chikhale).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2014.06.011

or generation of undesirable byproducts. Cyclodesulfurization of an intermediary thiourea may involve a toxic heavy-metal oxide (Kroeber et al., 1994) potentially explosive oxidant (Ogura et al., 1981) or transition metal (Chang et al., 1986) to facilitate cyclization. Previously reported methods to generate 2-aminobenzoxazoles directly from 2-aminophenols may require the preparation of a thioisocyanate (Wishart et al., 2003), *N*-cyanodithioimido carbonate (Tian et al., 2005), or chloroformadinium salt (Heinelt et al., 2004) prior to cyclization. 2-Aminobenzoxazoles have also been prepared directly from benzoxazoles using chloroamines (Wittenbrook, 1975) or formamides (El-Faham et al., 2006) as amine substitutes. 2-Aminobenzoxazoles can also be prepared from 2-chlorobenzoxazoles by reaction with hydrazine hydrate, ammonia, or amines (Sam and Plampin, 1964). Benzoxazol-2-amine is either obtained *via* reaction with concentrated ammonia (Doeller, 1939) or with ammonia in methanol. *N*-Alkyl- and *N*-arylbenzoxazol-2-amines are formed in a solvent-free reaction of 2-chlorobenzoxazoles and amines (Takahashi and Koshiro, 1959; Patil and Townsend, 1971). Alternatively, the reaction is carried out in aqueous solution (King and Acheson, 1949; Wamhoff and Materne, 1973) refluxing benzene or toluene (Ried and Schmidt, 1964), 1,1,2,2-tetrachloroethane (Zinner and Niendorf, 1956) or acetonitrile/triethylamine (Holan et al., 1967). Dimethylformamide is found not suitable since *N*,*N*-dimethylbenzoxazol-2-amine is formed after prolonged heating (Zare et al., 2010). A continued interest has led to the development of a wide variety of synthetic methods and new reagents for the synthesis of these compounds. Many of these methods have major drawbacks such as use of expensive chemicals, poor yield, hazardous reagents, solvents, tedious work-up procedures and failures in synthetic method.

There has been a rapid and extensive growth in the development of catalysts, novel reagents for the synthesis of these compounds for organic, inorganic and pharmaceutical use. Need for a new, efficient, reusable, economic and eco-friendly catalyst has led to the development of polymer bound catalysts. They are used in solution phase, solid phase synthesis, and microwave assisted synthesis because these methods offer benefits such as enhanced reaction rate, greater selectivity, ease at experimental work-up and comparatively high yields. These are of two types; soluble and insoluble polymer based, depending on the nature of polymer bound catalyst. The experimental work-up such as, washing, filtration, and isolation is easier with polymer bound catalyst of insoluble nature. An ideal one would act as a solvent and catalyst; however such examples are rare like ionic liquids, carbon dioxide, micellar systems etc. Poly (ethylene glycols) bound catalysts have been reported earlier by Wang et al. and Zare et al., for the synthesis of carboxyl pheneoxyacetic acid derivatives under solvent free conditions and acylals in the presence of solvents, respectively (Zare et al., 2010; Kidwai et al., 2010). Recently various new catalysts are reported for the synthesis of benzazoles such as CAN supported PEG (Rao et al., 2004), microwave assisted synthesis (Mohammadpoor-Baltork et al., 2008), and silica sulfuric acid catalyst (Mohammadpoor-Baltork et al., 2008), but for the synthesis of 2-aminobenzoxazoles these methods have some serious drawbacks relating to low substrate tolerance, low yield, weak selectivity and long reaction times.

Earlier in our lab the use of silica gel as a green catalyst for the synthesis of benzodiazepines (Chikhale and Khedekar, 2013) and substituted dihydropyrimidines was reported (Chikhale et al., 2009). Herein, we report the synthesis of 2-aminobenzoxazoles and various other derivatives of benzoxazole employing poly (ethylene glycol)-bound sulfonic acid (PEG-SO_3H) that acts concurrently as reaction promoter and reaction solvent (Fig. 1).

2. Experimental

2.1. Materials and methods

The uncorrected melting and boiling points of compounds were determined by the open tube capillary method using Thermonik precision apparatus (model-C-PMP-2, Mumbai, India), in Celsius scale. The purity of the compounds was verified by precoated TLC plates (E-Merck Kieselgel 60 F254). IR spectra were recorded using KBr pellets on a Perkin–Elmer 337 Spectrophotometer from Perkin–Elmer International Incorporation, Rorkreuz, Switzerland (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded on a Bruker W.M. 400 Spectrometer (Bruker AG, Fallanden, Switzerland) at 360 MHz using tetramethylsilane (TMS) as internal standard. (Chemical shifts in δ ppm). Mass spectra (FAB-MS) were recorded on 70 V on a Jeol D-300 spectrophotometer (Jeol Ltd., Tokyo, Japan) and elemental analysis was carried out using a FLASH EA 1112 CHN analyzer (Thermo Finngen, Italy).

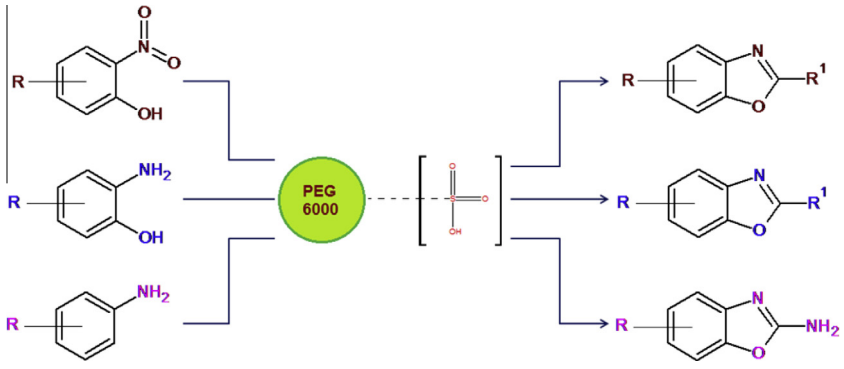


Figure 1 Diagrammatic representation of synthesis of 2-aminobenzoxazoles and various other derivatives of benzoxazole employing poly (ethylene glycol)-bound sulfonic acid (PEG-SO_3H).

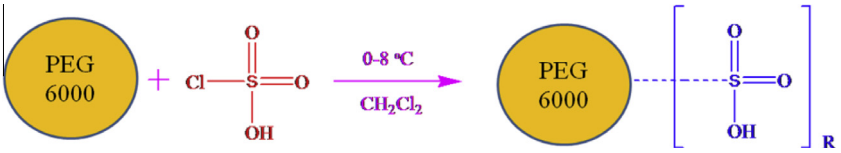


Figure 2 Diagrammatic representation of synthesis of poly (ethylene glycol)-bound sulfonic acid (PEG-SO_3H).

Table 1 Effect of different amounts of PEG-SO_3H on the reaction time and % yields of benzazoles in chloroform at normal atmospheric pressure.

Sr. No.	Amount of PEG-SO_3H	Time (min)	Yield (%)	Solvent
Scheme 1				
1	0.1 g (~0.83 mol%)	450	70	Chloroform
2	0.15 g (~1.25 mol%)	420	78	Chloroform
3	0.2 g (~1.65 mol%)	300	85	Chloroform
4	0.25 g (~2.1 mol%)	300	85	Chloroform
Scheme 2				
1	0.1 g (~0.83 mol%)	600	50	Dioxane + Chloroform
2	0.15 g (~1.25 mol%)	540	60	Dioxane + Chloroform
3	0.2 g (~1.65 mol%)	360	80	Dioxane + Chloroform
4	0.25 g (~2.1 mol%)	360	80	Dioxane + Chloroform
Scheme 3				
1	0.1 g (~0.83 mol%)	558	65	Chloroform
2	0.15 g (~1.25 mol%)	480	70	Chloroform
3	0.2 g (~1.65 mol%)	420	80	Chloroform
4	0.25 g (~2.1 mol%)	378	80	Chloroform

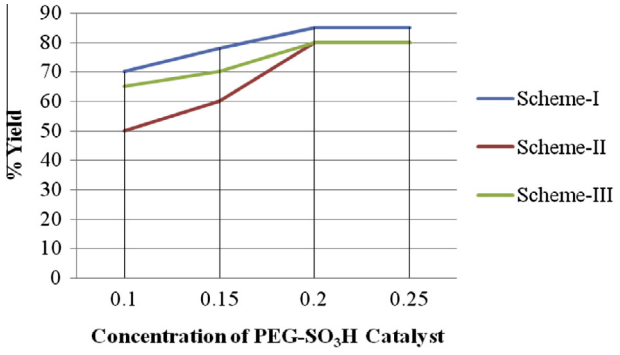


Figure 3 Study of % yield of the different class of products obtained against concentration of PEG-SO_3H.

2.2. Preparation of poly ethylene glycol (PEG)-bound sulfonic acid catalyst

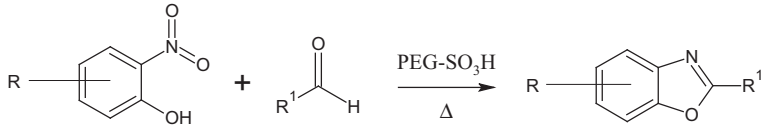
To a solution of poly (ethylene glycol)-6000 (1 mmol) in dichloromethane (15 mL) was added chlorosulfonic acid (10 mmol) at cold temperature (0–8 °C). The resulting solution was stirred mechanically at 20 °C for 16 h, and then concentrated under reduced pressure. Diethyl ether was added and the precipitated product was washed three times to give PEG-SO_3H (Fig. 2). ^{1}H NMR (400 MHz, CDCl3): d 12.85 (s, 1H, SO_3H), 4.23 (s, 2H, CH_2SO_3H), 3.49–3.66 (m, PEG).

In order to determine the amount of catalysts required for carrying out these reactions, another study was carried out involving different concentrations of catalysts for individual sets of reactions i.e., for substituted benzoxazole derivatives. The control study was carried out for representative reactions from each series. The first example involved the conversion of phenylurea into 2-aminobenzoxazole derivatives using different concentrations; the study was carried out as given in Table 1. The comparative study of the required concentration and time for completion of reaction was made (Fig. 3).

2.3. General procedure for the synthesis of benzoxazole derivatives

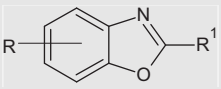
2.3.1. General procedure for the synthesis of substituted benzoxazole derivatives starting from substituted o-nitro phenols and substituted aldehydes (Scheme 1)

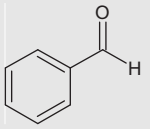
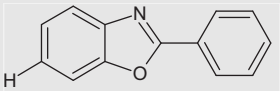
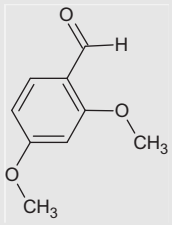
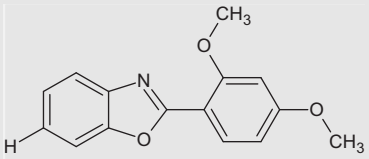
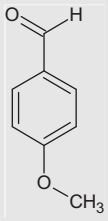
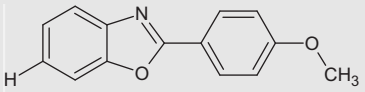
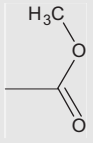
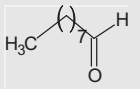
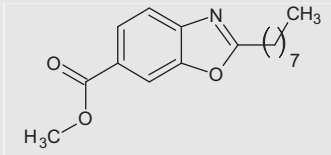
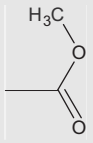
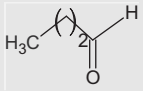
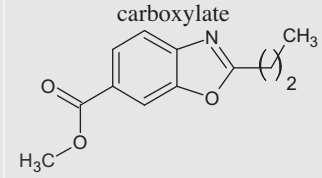
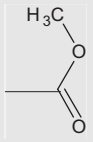
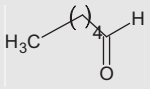
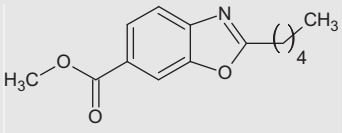
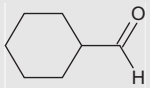
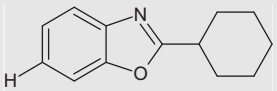
A solution of substituted *o*-nitro phenols (10 mmol) in a minimal quantity of chloroform was prepared and transferred into a three-neck round bottom flask. A spiral condenser, overhead stirrer and dropping funnel were attached to the reaction flask. PEG-SO_3H (2.1 mmol) was added with stirring for 30 min subsequently substituted aldehydes (10 mmol) were added *via* a



Scheme 1 Synthesis of substituted benzoxazole derivatives starting from substituted *o*-nitro phenols and substituted aldehydes.

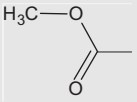
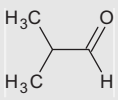
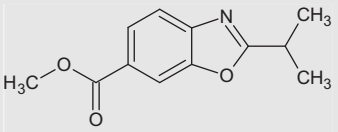
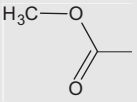
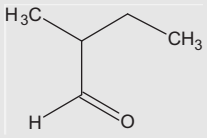
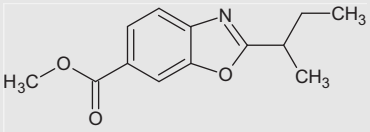
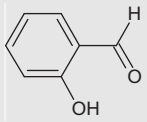
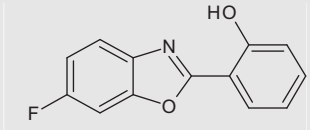
Table 2 Synthesis of substituted benzoxazole derivatives starting from substituted *o*-nitro phenols and substituted aldehydes.



Entry	R	R1	Product	Yield (%)	mp (°C)
1	H		 2-Phenyl-1,3-benzoxazole	94	136–138
2	H		 2-(2,4-Dimethoxyphenyl)-1,3-benzoxazole	92	210–212
3	H		 2-(4-Methoxyphenyl)-1,3-benzoxazole	95	165–167
4			 Methyl 2-octyl-1,3-benzoxazole-6-carboxylate	90	150–152
5			 Methyl 2-propyl-1,3-benzoxazole-6-carboxylate	90	132–135
6			 Methyl 2-pentyl-1,3-benzoxazole-6-carboxylate	94	121–124
7	H		 2-Cyclohexyl-1,3-benzoxazole	93	163–165

(*continued on next page*)

Table 2 (*continued*)

Entry	R	R1	Product	Yield (%)	mp (°C)
8			 2-(Propan-2-yl)-1,3-benzoxazole	98	137–139
9			 Methyl 2-(butan-2-yl)-1,3-benzoxazole-6-carboxylate	95	142–144
10	F		 2-(6-Fluoro-1,3-benzoxazol-2-yl)phenol	90	129–131

dropping funnel over a period of 30 min and further heated for 4–6 h at 50–60 °C. The reaction mixture was cooled to room temperature and the resulting solid mixture was washed with strong ammonia solution and filtered to remove catalyst. The solution was evaporated under vacuum (Scheme 1). The resulting products were recrystallized from rectified spirit to obtain substituted 2-aminobenzothiazoles (Table 2).

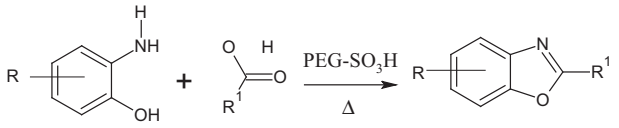
2.3.1.1. 2-Phenyl-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.1 from *o*-nitro phenol and benzaldehyde employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.5. ^{1}H NMR: δ 8.30–8.32 (m, 3H); 8.1 (dd, J = 1.2, 7.1 Hz, 1H); 7.8 (d, 8.3 Hz, 1H); 7.5 (m, 3H); 7.3 (d, 8.2 Hz, 1H). ^{13}C NMR: δ 166.6, 165.5, 150.4, 146.0, 132.1, 129.0, 127.9, 127.0, 126.5, 126.3, 119.5, 112.2. HRMS (M^+) Calculated: 195.2166, Found: 195.200.

2.3.1.2. 2-(2,4-Dimethoxyphenyl)-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.1 from *o*-nitro phenol and dimethoxy benzaldehyde employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.3. ^{1}H NMR: δ 8.26 (s, 1H); 8.15 (d, J = 8.8 Hz, 1H); 8.07 (dd, J = 1.3, 7.1 Hz, 1H); 7.8 (d, J = 8.4 Hz, 1H); 6.66 (dd, J = 2.1, 6.5 Hz, 1H); 6.63 (d, J = 2.1 Hz, 1H); 4.05 (s, 3H); 4.0 (s, 1H); 3.9 (s, 3H). ^{13}C NMR: δ 166.8, 164.3, 164.1, 160.3, 149.7, 146.3, 132.8, 126.3, 126.0, 119.3, 111.8, 108.4, 105.5, 99.1, 56.2, 55.6, 52.2. HRMS (M^+) Calculated: 255.2686, Found: 255.2700.

2.3.1.3. 2-(4-Methoxyphenyl)-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.1 from *o*-nitro phenol and para-methoxy benzaldehyde employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.3; ^{1}H NMR: δ 8.26–8.23 (3H, m); 8.10 (1H, dd, J = 8.4, 1.5 Hz); 7.76 (1H, d, J = 8 Hz); 7.07 (2H, m); 3.99 (3H, s); 3.93 (1H, s). ^{13}C NMR: δ 166.7, 165.5, 162.8, 150.3, 146.3, 129.8, 126.5, 126.3, 119.0, 114.4, 112.0, 55.5, 52.3. HRMS (M^+) Calculated: 225.2426 Found 225.2312.

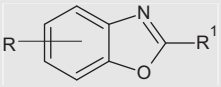
2.3.1.4. Methyl 2-octyl-1,3-benzoxazole-6-carboxylate. It was synthesized using the procedure given in Section 2.3.1 from *o*-nitro phenol methyl benzoate and octanal employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.4; ^{1}H NMR: δ 8.18 (d, J = 1.2 Hz, 1H); 8.05 (dd, J = 1.4 Hz, 7.0 Hz, 1H); 7.69 (d, J = 8.3 Hz, 1H); 4.0 (s, 3H); 2.95 (t, J = 7.6 Hz, 2H); 1.88 (q, J = 7.4 Hz, 2H), 1.28–1.46 (m, 10H); 0.87 (t, J = 6.7 Hz, 3H). ^{13}C NMR: δ 170.2, 166.7, 150.4, 145.3, 126.5, 125.9, 119.0, 111.9, 52.3, 31.7, 29.1, 29.0, 28.7, 26.6, 22.6, 14.0. HRMS (M^+) Calculated: 289.3694, Found: 289.3724.

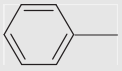
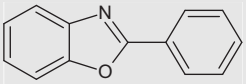
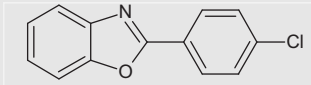
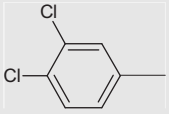
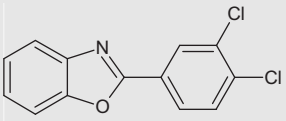
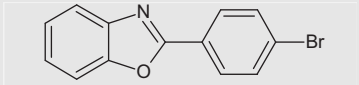
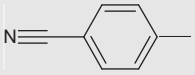
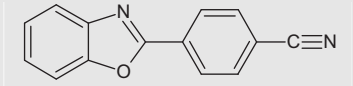
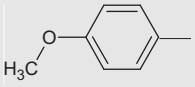
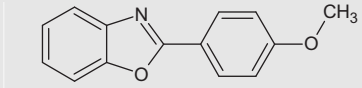
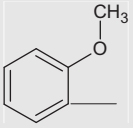
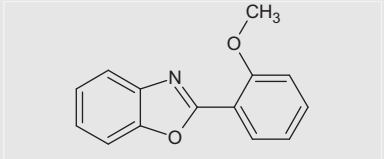
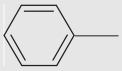
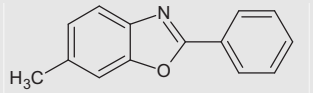
2.3.1.5. Methyl 2-propyl-1,3-benzoxazole-6-carboxylate. It was synthesized using the procedure given in Section 2.3.1 from *o*-nitro phenol methyl benzoate and propanal employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.4; ^{1}H NMR: δ 8.16 (d, J = 1.3 Hz, 1H), 8.05–8.02 (dd, J = 1.51, 6.7 Hz, 1H), 7.69–7.67 (d, J = 8.2 Hz, 1H), 3.95 (s, 3H), 2.96–2.92 (t, J = 7.4 Hz, 2H), 1.96–1.91 (m, 2H), 1.08–1.04 (t,



Scheme 2 Synthesis of substituted benzoxazole derivatives starting from substituted 2-amino phenols and substituted benzoic acids.

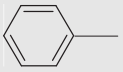
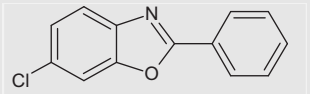
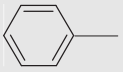
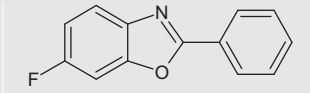
Table 3 Synthesis of substituted benzoxazole derivatives starting from substituted 2-amino phenols and substituted benzoxazoic acids.



Entry	R	R^1	Product	Yield (%)	mp (°C)
11	H		 2-Phenyl-1,3-benzoxazole	95	136–138
12	H		 2-(4-Chlorophenyl)-1,3-benzoxazole	97	148–150
13	H		 2-(3,4-Dichlorophenyl)-1,3-benzoxazole	98	144–145
14	H		 2-(4-Bromophenyl)-1,3-benzoxazole	92	157–158
15	H		 4-(1,3-Benzoxazol-2-yl)benzonitrile	98	203–206
16	H		 2-(4-Methoxyphenyl)-1,3-benzoxazole	97	165–167
17	H		 2-(2-Methoxyphenyl)-1,3-benzoxazole	97	53–55
18	4-Me		 6-Methyl-2-phenyl-1,3-benzoxazole	95	93–95

(*continued on next page*)

Table 3 (*continued*)

Entry	R	R^1	Product	Yield (%)	mp (°C)
19	4-Cl		 6-Chloro-2-phenyl-1,3-benzoxazole	90	107–108
20	4-F		 6-Fluoro-2-phenyl-1,3-benzoxazole	98	109–110

J = 7.42 Hz, 3H). ^{13}C NMR: δ 170.0, 166.7, 150.4, 145.3, 126.5, 125.8, 119.0, 111.9, 52.2, 30.6, 20.0, 13.7. HRMS (M^+) Calculated: 289.3694, Found: 289.3724.

2.3.1.6. Methyl 2-pentyl-1,3-benzoxazole-6-carboxylate. It was synthesized using the procedure given in Section 2.3.1 from *o*-nitro phenol methyl benzoate and pentanal employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.4; ^{1}H NMR: δ 8.16 (d, J = 0.9 Hz, 1H), 8.04–8.02 (dd, J = 1.5, 6.87 Hz, 1H), 7.69–7.67 (d, J = 8.3 Hz, 1H), 3.94 (s, 3H), 2.97–2.93 (t, J = 7.6 Hz, 2H), 1.94–1.86 (m, 2H), 1.47–1.35 (m, 4H), 0.93–0.89 (t, J = 7 Hz, 3H). ^{13}C NMR: δ 170.2, 166.7, 150.4, 145.3, 125.9, 119.0, 111.9, 52.3, 31.2, 29.6, 28.7, 26.2, 22.2, 13.8. HRMS (M^+) Calculated: 247.2896, Found: 247.2900.

2.3.1.7. 2-Cyclohexyl-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.1 from *o*-nitro phenol and cyclohexanal employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.3. ^{1}H NMR: δ 8.17 (d, J = 1 Hz, 1H); 8.04 (dd, J = 1 Hz, 7.1 Hz, 1H); 7.7 (d, J = 8.3 Hz, 1H); 3.96 (s, 1H); 2.97 (m, 1H); 2.18 (m, 2H); 1.88 (m, 2H); 1.72 (m, 3H); 1.27 (m, 3H). ^{13}C NMR: δ 173.2, 166.7, 150.2, 145.3, 126.5, 125.8, 119.1, 111.9, 52.2, 38.0, 30.3, 25.6, 25.5. HRMS (M^+) Calculated: 201.2643, Found: 201.2710.

2.3.1.8. 2-(Propan-2-yl)-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.1 from *o*-nitro phenol methyl benzoate and isopropanal employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.5; ^{1}H NMR: δ 8.17 (s, 1H), 8.05–8.03 (d, J = 8.33 Hz, 1H), 7.71–7.69 (d, J = 8.31 Hz, 1H), 3.95 (s, 3H), 3.31–3.24 (m, 1H), 1.49–1.47 (d, J = 7.6 Hz, 6H). ^{13}C NMR: δ 174.0, 166.6, 50.3, 145.2, 126.5, 125.8, 119.1, 111.9, 52.2, 28.9, 20.1. HRMS (M^+) Calculated: 219.2365, Found: 219.2371.

2.3.1.9. Methyl 2-(butan-2-yl)-1,3-benzoxazole-6-carboxylate. It was synthesized using the procedure given in Section 2.3.1 from *o*-nitro phenol methyl benzoate and isobutanal employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.4; ^{1}H NMR: δ 8.17 (1H, s); 8.03 (1H, d, J = 8 Hz); 7.69 (1H, d, J = 8 Hz); 3.94 (3H, s); 3.08 (1H, sextuplet, J = 6 Hz); 1.99–1.74 (2H, m); 1.44 (3H, d, J = 7 Hz); 0.96 (3H, t, J = 7 Hz). ^{13}C NMR: δ 173.5, 166.7, 150.3, 145.2, 126.5, 125.8, 119.1, 112.0, 52.3, 35.8, 27.9, 17.7, 11.5. HRMS (M^+) Calculated: 233.2631, Found: 233.2733.

2.3.1.10. 2-(6-Fluoro-1,3-benzoxazol-2-yl)phenol. It was synthesized using the procedure given in Section 2.3.1 from meta fluro-3-nitro phenol and 2-hydroxy benzaldehyde employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.5; ^{1}H NMR: δ 8.23–8.26 (m, 2H); 7.70–7.74 (m, 1H); 7.55–7.58 (m, 3H); 7.33–7.35 (dd, J = 2.4 Hz, 5.6 Hz, 1H); 7.13–7.16 (m, 1H). ^{13}C NMR: δ 131.5, 128.9, 127.4, 126.8, 120.3, 120.2, 112.6, 112.4, 98.8, 98.5. HRMS (M^+) Calculated: 211.2160, Found: 211.2231.

2.3.2. General procedure for synthesis of substituted benzoxazole derivatives starting from substituted 2-amino phenols and substituted benzoic acids (Scheme 2)

A solution of substituted 2-amino phenols (10 mmol) was prepared in a mixture of Dioxane:Chloroform (1:1) arranged in a three neck flask, to it a solution of substituted benzoic acid (10 mmol) in chloroform was added drop wise over a period of 1 h with constant stirring. To this mixture PEG-SO_3H (2.1 mmol) was added and the reaction was carried out for 5–6 h at 60–65 °C, progress of reaction was monitored by TLC. After completion of reaction as determined by TLC, the reaction mixture was cooled to room temperature and the resulting solid was washed with strong ammonia solution and filtered to remove catalyst, then dried under vacuum (Scheme 2). The resulting products were recrystallized from rectified spirits to obtain substituted 2-aminobenzoxazoles (Table 3).

2.3.2.1. 2-Phenyl-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.2 from 2-amino phenol and benzoic acid employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.5; ^{1}H NMR: δ 8.32 (dd, 2H, J = 5.6 Hz, J = 2.1 Hz), 7.79–7.86 (m, 1H), 7.53–7.67 (m, 4H), 7.36–7.44 (m, 2H). ^{13}C NMR: δ 163.1, 150.8, 142.2, 131.4, 128.9, 127.6, 127.2, 125.1, 124.6, 120.0, 110.6. HRMS (M^+) Calculated: 195.0684, Observed: 195.0683.

2.3.2.2. 2-(4-Chlorophenyl)-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.2 from 2-amino phenol and para chloro benzoic acid employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.4; ^{1}H NMR: δ 8.22 (d, 2H, J = 7.8 Hz), 7.77–7.84 (m, 1H), 7.57–7.65 (m, 1H), 7.52 (d, 2H, J = 7.8 Hz), 7.36–7.44 (m, 2H). ^{13}C NMR: δ 162.1, 150.8, 142.0, 137.8, 129.3, 128.9, 125.7, 125.4, 124.8, 120.1, 110.6. HRMS (M^+) Calculated: 229.6617, Found: 229.7001.

2.3.2.3. 2-(3,4-Dichlorophenyl)-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.2 from 2-amino phenol and 3,4-dichloro benzoic acid employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.5; ^{1}H NMR: δ 8.37 (d, 1H, J = 1.8 Hz), 8.09 (dd, 1H, J = 8.2 Hz, J = 1.8 Hz), 7.77–7.83 (m, 1H), 7.58–7.65 (m, 2H), 7.38–7.45(m, 2H). ^{13}C NMR: δ 160.9, 150.8, 141.9, 135.9, 133.5, 131.1, 129.3, 127.1, 126.5, 125.7, 125.0, 120.3, 110.7. HRMS (M^+) Calculated: 264.1067, Found: 264.120.

2.3.2.4. 2-(4-Bromophenyl)-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.2 from 2-amino phenol and 4-bromo benzoic acid employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.5; ^{1}H NMR: δ 8.16 (m, 2H), 7.78–7.84 (m, 1H), 7.68–7.75 (m, 2H), 7.59–7.66 (m, 1H), 7.37–7.45 (m, 2H). ^{13}C NMR: δ 162.1, 150.8, 142.0, 132.3, 129.0, 126.3, 126.1, 125.4, 124.8, 120.1, 110.7. HRMS (M^+) Calculated: 274.1127, Found: 274.1221.

2.3.2.5. 4-(1,3-Benzoxazol-2-yl)benzonitrile. It was synthesized using the procedure given in Section 2.3.2 from 2-amino phenol and 4-cyano benzoic acid employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.4; ^{1}H NMR: δ 8.37 (d, 2H, J = 8.5 Hz), 7.80–7.87 (m, 3H), 7.60–7.68 (m, 1H), 7.39–7.49 (m, 2H). ^{13}C NMR: δ 160.6, 150.9, 141.9, 132.7, 131.1, 128.0, 126.2, 125.1, 120.6, 118.2, 114.7, 110.9. HRMS (M^+) Calculated: 220.2261, Found: 220.2301.

2.3.2.6. 2-(4-Methoxyphenyl)-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.2 from 2-amino phenol and 4-methoxy benzoic acid employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.4; ^{1}H NMR: δ 8.13 (d, 2H, J = 8.2 Hz), 7.75–7.80 (m, 1H), 7.56–7.61 (m, 1H), 7.31–7.40 (m, 2H), 7.06 (d, 2H, J = 8.2 Hz), 3.91 (s, 3H). ^{13}C NMR: δ 163.2, 162.3, 150.7, 142.3, 129.4, 124.6, 124.4, 119.7, 119.6, 114.4, 110.4, 55.5. HRMS (M^+) Calculated: 225.2426, Found: 225.2312.

2.3.2.7. 2-(2-Methoxyphenyl)-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.2 from 2-amino phenol and 2-methoxy benzoic acid employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.3; ^{1}H NMR: δ 8.18 (dd, 1H, J = 7.7 Hz, J = 1.8 Hz), 7.83–7.90 (m, 1H), 7.60–7.66 (m, 1H), 7.52–7.58 (m, 1H), 7.35–7.42 (m, 2H), 7.11–7.17 (m, 2H), 4.06 (s, 3H). ^{13}C NMR: δ 161.6, 158.5, 150.4, 142.2, 132.8, 131.3, 124.9, 124.3, 120.7, 120.3, 116.2, 112.1, 110.5, 56.2. HRMS (M^+) Calculated: 225.2426, Found: 225.2322.

2.3.2.8. 6-Methyl-2-phenyl-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.2 from 4-methyl-2-amino phenol and benzoic acid employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.3; ^{1}H NMR: δ 8.24–8.31 (m, 2H), 7.68 (d, 1H, J = 8.2 Hz), 7.51–7.58 (m, 3H), 7.40 (t, 1H, J = 0.6 Hz,), 7.19 (dd, 1H, J = 8.0 Hz, J = 1.5 Hz, J = 0.6 Hz), 2.53 (s, 3H). ^{13}C NMR: δ 162.6, 151.1, 140.0, 135.6, 131.3, 128.9, 127.5, 127.4, 125.8, 119.4, 110.8, 21.8. HRMS (M^+) Calculated: 209.2432, Found: 209.2400.

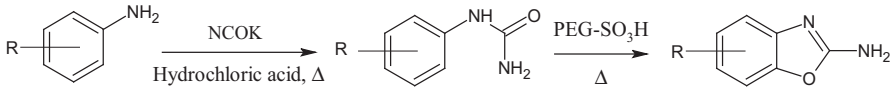
2.3.2.9. 6-Chloro-2-phenyl-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.2 from 4-chloro-2-amino phenol and benzoic acid employing PEG-SO_3H. TLC (1:1 CH_2Cl_2:Hexane), R_f = 0.3; ^{1}H NMR: δ 8.16–8.23 (m, 2H), 7.64 (d, 1H, J = 8.5 Hz), 7.55 (d, 1H, J = 1.9 Hz), 7.45–7.57 (m, 3H), 7.30 (dd, 1H, J = 8.5 Hz, J = 1.9 Hz. ^{13}C NMR: δ 163.7, 151.0, 140.9, 131.8, 130.7, 129.0, 127.7, 126.8, 125.3, 120.5, 111.2. HRMS (M^+) Calculated: 229.6617, Found: 229.8901.

2.3.2.10. 6-Fluoro-2-phenyl-1,3-benzoxazole. It was synthesized using the procedure given in Section 2.3.2 from 4-fluro-2-amino phenol and benzoic acid employing PEG-SO_3H. TLC (1:1 CH_2Cl_2: Hexane), R_f = 0.3; ^{1}H NMR: δ 8.20–8.28 (m, 2H), 7.72 (dd, 1H, J = 8.8 Hz, J = 4.9 Hz), 7.50–7.59 (m, 3H), 7.33 (dd, 1H, J = 8.0 Hz, J = 2.3 Hz), 7.13(td, 1H, J = 8.8 Hz, J = 2.3 Hz). ^{13}C NMR: 138.4, 131.6, 128.9, 127.5, 126.9, 120.3. HRMS (M^+) Calculated: 213.2071, Found: 213.2082.

2.3.3. General procedure for synthesis of substituted 2-amino benzoxazole derivatives starting from substituted anilines (Scheme 3)

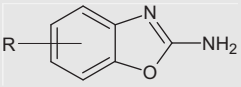
Synthesis of substituted benzoxazol-2-amine or substituted 2-aminobenzoxazoles was carried out in two steps. First step involves the synthesis of substituted phenylurea from parent anilines followed by PEG-SO_3H promoted cyclization. Substituted aniline (10 mmol) was added to a round bottom flask containing water. To it was added conc. HCl (10 ml), the mixture was warmed for about 10 min followed by addition of potassium cyanate (10 mmol) and was stirred for 1 h. The solid was allowed to precipitate (at low temperature 0–5 °C), the precipitate so obtained was filtered and dried. A solution of substituted phenylurea (10 mmol) was prepared in chloroform, to it PEG-SO_3H (2.1 mmol) was added. The reaction mixture was stirred for about 6–7 h at 80–90 °C, progress and completion of reaction were monitored by the TLC method. After completion of the reaction it was allowed to cool to room temperature. The catalyst was filtered out. Filtrate was made basic by addition of ammonia solution leading to precipitation of the product which was collected and further recrystallized from rectified spirits (Scheme 3, Table 4).

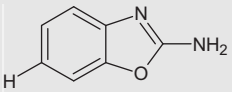
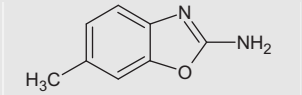
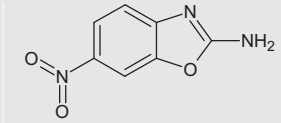
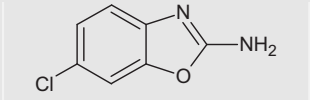
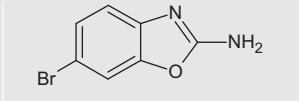
2.3.3.1. 1,3-Benzoxazol-2-amine. Synthesis of 1,3-benzoxazol-2-amine was carried out in two steps. Aniline (10 mmol) was added to a round bottom flask containing water. To it was added conc. HCl (10 ml), the mixture was warmed for about 10 min followed by addition of potassium cyanate (10 mmol) and was stirred for 1 h. The solid was allowed to precipitate (at low temperature 0–5 °C), the precipitate was filtered and dried.



Scheme 3 Synthesis of substituted 2-amino benzoxazole derivatives starting from substituted anilines.

Table 4 Synthesis of substituted 2-amino benzoxazole derivatives starting from substituted anilines.



Entry	R	Product	Yield (%)	mp (°C)
21	H	 1,3-Benzoxazol-2-amine	97	128–132
22	CH_3	 6-Methyl-1,3-benzoxazol-2-amine	95 92	112–114
23	NO_2	 6-Nitro-1,3-benzoxazol-2-amine	97	150–152
24	Cl	 6-Chloro-1,3-benzoxazol-2-amine	93	180–185
25	Br	 6-Bromo-1,3-benzoxazol-2-amine		172–174

A solution of phenyl urea (10 mmol) was prepared in chloroform, to it PEG-SO_3H (2.1 mmol) was added. The reaction mixture was stirred for about 6–7 h at 80–90 °C, progress and completion of reaction were monitored by the TLC method. After completion of the reaction it was allowed to cool to room temperature. The catalyst was filtered out. Filtrate was made basic by addition of ammonia solution leading to precipitation of the product which was collected and further recrystallized from rectified spirits. Yield: 97%, mp: 128–132 °C, TLC (1:1; CH_2Cl_2:Hexane), R_f = 0.5.

2.3.3.2. 6-Methyl-1,3-benzoxazol-2-amine. Synthesis of 6-methyl-1,3-benzoxazol-2-amine was carried out in two steps, 4-methyl aniline (10 mmol) was added to a round bottom flask containing water. To it was added conc. HCl (10 ml), the mixture was warmed for about 10 min followed by addition of potassium cyanate (10 mmol) and was stirred for 1 h. The solid was allowed to precipitate (at low temperature 0–5 °C), the precipitate was filtered and dried.

A solution of tolylurea (10 mmol) was prepared in chloroform, to it PEG-SO_3H (2.1 mmol) was added. The reaction mixture was stirred for about 6–7 h at 80–90 °C, progress and completion of reaction were monitored by the TLC method. After completion of the reaction it was allowed to cool to room temperature. The catalyst was filtered out. Filtrate was made basic by addition of ammonia solution leading to precipitation of the product which was collected and further recrystallized from rectified spirits. Yield: 95%, mp: 112–114 °C, TLC (1:1; CH_2Cl_2:Hexane), R_f = 0.5.

2.3.3.3. 6-Nitro-1,3-benzoxazol-2-amine. Synthesis of 6-nitro-1,3-benzoxazol-2-amine was carried out in two steps, para-nitro aniline (10 mmol) was added to a round bottom flask containing water. To it was added conc. HCl (10 ml), the mixture was warmed for about 10 min followed by addition of potassium cyanate (10 mmol) and was stirred for 1 h. The solid was allowed to precipitate (at low temperature 0–5 °C), the precipitate was filtered and dried.

A solution of para-nitrophenyl urea (10 mmol) was prepared in chloroform, to it PEG-SO_3H (2.1 mmol) was added. The reaction mixture was stirred for about 6–7 h at 80–90 °C, progress and completion of reaction were monitored

by the TLC method. After completion of the reaction it was allowed to cool to room temperature. The catalyst was filtered out. Filtrate was made basic by addition of ammonia solution leading to precipitation of the product which was collected and further recrystallized from rectified spirits. Yield: 92%, mp: 150–152 °C, TLC (1:1; CH_2Cl_2:Hexane), R_f = 0.4.

2.3.3.4. 6-Chloro-1,3-benzoxazol-2-amine. Synthesis of 6-chloro-1,3-benzoxazol-2-amine was carried out in two steps, para-chloro aniline (10 mmol) was added to a round bottom flask containing water. To it was added conc. HCl (10 ml), the mixture was warmed for about 10 min followed by addition of potassium cyanate (10 mmol) and was stirred for 1 h. The solid was allowed to precipitate (at low temperature 0–5 °C) the precipitate was filtered and dried.

A solution of para-chlorophenyl urea (10 mmol) was prepared in chloroform, to it PEG-SO_3H (2.1 mmol) was added. The reaction mixture was stirred for about 6–7 h at 80–90 °C, progress and completion of reaction were monitored by the TLC method. After completion of the reaction it was allowed to cool to room temperature. The catalyst was filtered out. Filtrate was made basic by addition of ammonia solution leading to precipitation of the product which was collected and further recrystallized from rectified spirits. Yield: 97%, mp: 180–185 °C, TLC (1:1; CH_2Cl_2:Hexane), R_f = 0.4.

2.3.3.5. 6-Bromo-1,3-benzoxazol-2-amine. Synthesis of 6-bromo-1,3-benzoxazol-2-amine was carried out in two steps, para-bromo aniline (10 mmol) was added to a round bottom flask containing water. To it was added conc. HCl (10 ml), the mixture was warmed for about 10 min followed by addition of potassium cyanate (10 mmol) and was stirred for 1 h. The solid was allowed to precipitate (at low temperature 0–5 °C), the precipitate was filtered and dried.

A solution of para-bromophenyl urea (10 mmol) was prepared in chloroform, to it PEG-SO_3H (2.1 mmol) was added. The reaction mixture was stirred for about 6–7 h at 80–90 °C, progress and completion of reaction were monitored by the TLC method. After completion of the reaction it was allowed to cool to room temperature. The catalyst was filtered out. Filtrate was made basic by addition of ammonia solution leading to precipitation of the product which was collected and further recrystallized from rectified spirits. Yield: 93%, mp: 172–174 °C, TLC (1:1; CH_2Cl_2:Hexane), R_f = 0.3.

3. Results and discussion

The present article describes a highly economical, facile and clean method for the synthesis of chemically and pharmaceutically important benzoxazole derivatives by employing poly (ethylene glycol) supported sulfonic acid (PEG-SO_3H) as a reusable catalyst. PEG acts as support for sulfonic acid as the catalyst as well as solvent medium. A study presented by Zare et. al., was taken into consideration to determine and optimize an optimal catalyst system for the synthesis of 2-aminobenzoxazole. Different molar concentrations of catalyst, duration of reaction, and use of solvent systems were used as presented in Table 1. It was observed that synthesis of 2-aminobenzoxazole was obtained in the highest yield of 97% at about 80–90 °C in the presence of a solvent system consisting of chloroform, instead of 78% when the reaction was carried out in the presence of PEG alone. The concentration of PEG-SO_3H needed was studied keeping solvent and temperature constant; it was found that use of ~2.1 mmol of catalyst gave optimum results. As the catalyst was recovered after each reaction, the ability to recycle the catalyst was investigated. After 3–4 cycles of use the% yield was hampered also the consistence of PEG-SO_3H has changed. However, it was found that up to 3 cycles the catalytic activity provided good yields of the reaction product. This encouraged the use of PEG-SO_3H in the synthesis of 2-amino derivatives of benzoxazole. A variety of substituents and methods were tested and two of these methods were optimized for their synthetic applicability. First, the synthesis uses 2-nitro phenols with aldehydes and second the synthesis involves 2-nitro phenols and carboxylic acids.

The first method involves the synthesis of benzoxazoles from substituted 2-nitro phenols and allyl or aryl aldehydes

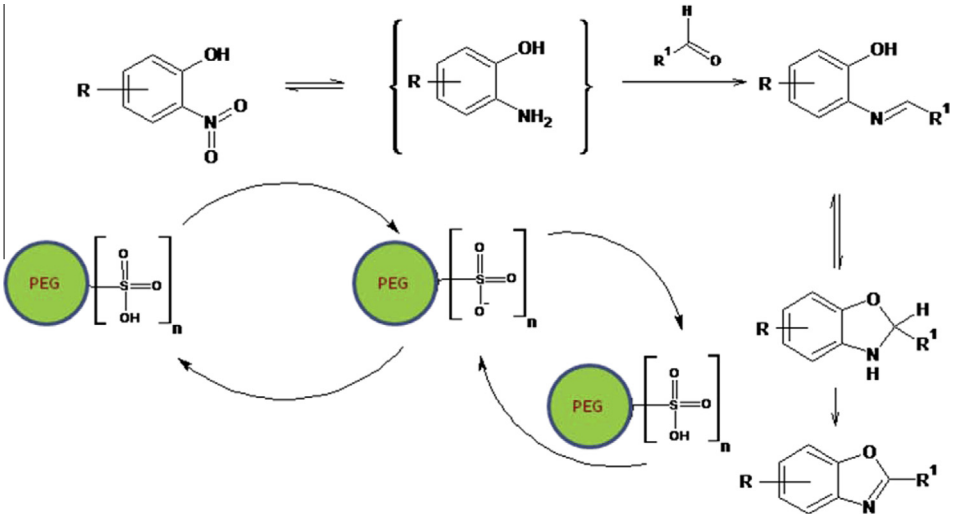


Figure 4 Predicted possible mechanism for synthesis of substituted benzoxazole derivatives starting from substituted *o*-nitro phenols and substituted aldehydes.

(Scheme 1). This method was optimized by use of chloroform as solvent medium along with PEG-SO_3H, 4–6 h at 50–60 °C for the synthesis of 2-aminobenzoxazole derivatives. The products were obtained in a range of 90–96% which is satisfactory, also for production on a large scale (Table 2). The products like allyl derivatives found application in the coating industry and production of olefins. In figure number four (Fig. 4) it is tried to explain predicted possible mechanism for the synthesis of substituted benzoxazole derivatives starting from substituted *o*-nitro phenols and substituted aldehydes. The second method involved the synthesis of benzoxazoles from 2-amino phenols and carboxylic acids (Scheme 2). This method was optimized by use of a solvent system consisting of Dioxane:Chloroform (1:1) at 60–65 °C for about 5–6 h. The % yield was found to be satisfactory in the range of 90–97% (Table 3).

In reference to Scheme 3, all compounds (Table 4) are known and widely used for scaffold synthesis. These compounds were synthesized in excellent yields as compared to other methods; however our method involves two steps. In the first step phenyl urea of respective anilines was synthesized followed by their cyclization employing PEG-SO_3H as a mild catalyst. Their physico-chemical properties are similar to those of the standard compounds which are commercially available.

All the synthesized compounds were analyzed by ^1H NMR, ^{13}C NMR and HR-MS for establishing their structures, compound 2.3.1.1. (Table 2, entry 1–10), compound 2.3.2.1. (Table 3, entry 11–20) and compound 2.3.3.1. (Table 4, entry 21–25) are compounds prepared by different methods hence their physico-chemical properties were studied and they were found to be identical to authentic samples prepared by different methods. This provided us with a new synthetic route to a variety of compounds and with the option of different substituents.

In summary, we have developed a more eco-friendly method to synthesize benzoxazole derivatives in excellent yields with high purity using a reusable PEG-SO_3H catalyst very economically.

Acknowledgments

RVC is thankful to Council of Scientific and industrial Research (CSIR) New Delhi, India for providing financial support in form of SRF: 09/128/0080/2011/EMR-I. PBK acknowledges financial support by University Grants Commission (UGC) New Delhi, India in form of Major Research Project 41-744/2012 (SR).

References

Chang, H.S., Yon, G.H., Kim, Y.H., 1986. Chem. Lett., 1291.
Cheung, M., Harris, P., Hasegawa, M., Ida, S., Kano, K., Nishigaki, N., 2002. PCT WO 02/44156A2.
Chikhale, R.V., Khedekar, P.B., 2013. Curr. Catal. 2, 111.
Chikhale, R.V., Bhole, R.P., Khedekar, P.B., Bhusari, K.P., 2009. Eur. J. Med. Chem. 44, 3645.
Clark, D., Eastwood, P., Harris, N., McCarthy, C., Morley, A., Pickett, S., 2000. PCT WO 00/49005.
Cox, C.D., Breslin, M.J., Whitman, D.B., Schreier, J.D., McGaughey, G.B., Bogusky, M.J., Roecker, A.J., Mercer, S.P., Bednar, R.A., Lemaire, W., Bruno, J.G., Reiss, D.R., Harrell, C.M., Murphy, K.L., Garson, S.L., Doran, S.M., Prueksaritanont, T., Coleman, P.J., 2010. J. Med. Chem. 53, 5320.
Doeller, W., 1939. Ber. Dtsch. Chem. Ges. 72, 2148.
El-Faham, A., Chebbo, M., Abdul-Ghani, M., Younes, G., 2006. J. Heterocycl. Chem. 43, 599.
Heinelt, U., Shultheis, D., Jeager, S., Lindenmaier, M., Pollex, A., Beckman, H., 2004. Tetrahedron 60, 9883.
Holan, G., Samuel, E.L., Ennis, B.C., Hinde, R.W., 1967. J. Chem. Soc. C, 20.
Jain, K., Shah, A., Bariwal, J., 2007. Bioorg. Med. Chem. 15, 1181.
Katz, L., Cohen, M., 1954. J. Org. Chem. 19, 758.
Kidwai, M., Jahan, A., Bhatnagar, D., 2010. J. Chem. Sci. 122, 607.
King, F.E., Acheson, R.M., 1949. J. Chem. Soc., 1396.
Kroeber, J., Tímar, T., Tompa, J., 1994. Synthesis, 1124.
Laibekman, A., Jantzen, H. M., Conley, L., Fretto, L., Scarborough, R., 2003. US 6667306B1.
Mccracken, R., Stillwell, W., 1991. Int. J. Parasitol. 21, 99.
Mohammadpoor-Baltork, I., Moghadam, M., Tangestaninejad, S., Mirkhani, V., Zolfigol, M.A., Hojati, S., 2008. J. Iran. Chem. Soc. 5, S65.
Muller, P., Huranus, R., Maier, R., Mark, M., Eisele, S., Budzinski, R., Thomas, L., Hallermayer, G., 1999. US Patent US 5919807.
Murugesan, D., Palaniappan, S., Perumal, Y., 2009. Biomed. Pharmacother. 63, 11.
O'Donnell, C.J., Rogers, B.N., Bronk, B.S., Bryce, D.K., Coe, J.W., Cook, K.K., Duplantier, A.J., Evrard, E., Hajos, M., Hoffmann, W.E., Hurst, R.S., Aklad, N., Mather, R.J., McLean, S., Nedza, F.M., ONeill, B.T., Peng, L., Qian, W., Rottas, M.M., Sands, S.B., Zhang, L., 2010. J. Med. Chem. 53, 1222.
Ogura, H., Mineo, S., Nakagawa, K., 1981. Chem. Pharm. Bull. 29, 1518.
Patil, V.D., Townsend, L., 1971. J. Heterocycl. Chem. 8, 503.
Rao, A., Chimirri, A., Ferro, S., Maria Monforte, A., Monforte, P., 2004. ARKIVOC 5, 147.
Ried, W., Schmidt, E., 1964. Justus Liebigs Ann. Chem. 676, 114.
Sam, J., Plampin, J., 1964. J. Pharm. Sci. 53, 538.
Sato, Y., Yamada, M., Kobayashi, K., Iwamatsu, K., Konno, F., Shudo, K., 1997. EP 806419 A1.
Seefelder, M., Leuchs, D., 1962. GB 913910.
Siddiqui, N., Rana, A., Khan, S., 2007. Bioorg. Med. Chem. Lett. 17, 4178.
Surleraux, D., Vendeville, S., Verschueren, W., De Bethune, M., De Kock, H., Tahri, A., 2002. WO 02/092595A1.
Takahashi, T., Koshiro, A., 1959. Chem. Pharm. Bull. 7, 720.
Tian, T., Ling, L., 2007. J. Chin. Chem. Soc. 54, 1369.
Tian, Z., Plata, W., Bhatia, A., 2005. Tetrahedron Lett., 8341.
Tsurumi, K., Hiramatsu, Y., Hayashi, M., Yamaguchi, I., 1973. Arzneimittelforschung 70, 261.
Vicini, P., Geronikaki, A., Incerti, M., 2003. Bioorg. Med. Chem. 11, 4709.
Vicini, P., Geronikaki, A., Incerti, M., 2008. Bioorg. Med. Chem. 16, 3714.
Walczynski, K., Guryn, R., Timmerman, H., 1999. IL Farmaco 54, 684.
Wamhoff, H., Materne, C., 1973. Justus Liebigs Ann. Chem., 573.
Wang, X., Li, Z., Da, Y., Chen, J., Wei, T., 2007. Synth. Commun. 29, 4153.
Wishart, N., Rudolph, A., Ritter, K., 2003. US Patent US2003/0109714 A1.
Wittenbrook, L., 1975. J. Heterocycl. Chem. 12, 37.
Yamato, M., Takeuchi, Y., Hattori, K., Hashigaki, K., 1984. Chem. Pharm. Bull. 32, 3053.
Yildiz-Oren, I., Yalcin, I., Aki-Saner, E., 2004. Eur. J. Med. Chem. 39, 291.
Yoshida, M., Hayakawa, I., Hayashi, N., 2005. Bioorg. Med. Chem. 15, 3328.
Zare, A., Hasaninejad, A., Roastami, E., Moosavi-zare, A.R., Trans, C., 2010. Chem. Chem. Eng. 17, 24.
Zinner, H., Niendorf, N., 1956. Chem. Ber. 89, 1012.